10^{-20} Joules as a Neuromolecular Quantum in Medicinal Chemistry: An Alternative Approach to Myriad Molecular Pathways?

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Abstract: The myriads of molecular pathways that have been measured to understand the physical bases of neuronal and other cellular functions have exceeded classical comprehension. In the tradition of Bohr and Schrodinger, the hypothesis is developed that molecular pathways are simply epiphenomenal transports of quanta with increments in the order of 10^{-20} J. Experimental measurements of photon emissions from cell cultures and the serial steps of phosphorylation in general molecular pathways and transformations in chromophores supported this contention. This discrete value is also associated with action potentials, intersynaptic events, the biophysical bases of membrane potentials, the numbers of action potentials per cell from magnetic energy potential, and the interionic distances around membranes. Consideration of information as discrete increments of energy may allow greater experimental control and external intervention of pathways relevant to medicinal chemistry.

Keywords: Neuroquantum, cell membranes, energy, 10^{-20} J, wave functions, molecular biology.

1. INTRODUCTION

Modern medical and biological sciences have replaced the perspective of the singularity of the whole organism with a matrix of multiple and often dissociated molecular pathways [1]. From either a correlational or reductionist approach to biological systems, the fundamental characteristics and patterns of larger organizations of matter in space-time reflect the smaller forms. The initial enthusiasm for molecular biology proposed by Schrödinger [2] as the quintessential approach to solve the challenges of medicinal biology has been dampened by the accelerating numbers of molecular pathways and the plethora of substitutions in these pathways by which the apparently "same" signalling occurs. In the frenzy to find "the molecular pathway", today's manifestation of Paul Erhlich's "magic bullet", we have forgotten Bohr's [3] suggestion that small amounts of energy involved with quantum theory mediate the features of cell functions.

There may be an intrinsic approximal unit of energy by which many if not all molecular pathways relevant to medicinal chemistry operate. One of these "quanta", in the order of 10^{-20} J, involves a chain of simple transformations of matter and energy across biological space and time. Consequently the numbers of multiple pathways and inordinate numbers of molecules involved with signalling are simply carriers or epiphenomena whose presence insures the accurate transmission of these digital quanta whose summations of events are reflected at larger and larger levels of organization. The support for the concept lies within the quantitative convergence with empirical measurements and the internal consistencies of the magnitudes of energy. Although traditions within the last few decades have embraced qualitative perspectives for reviews and developments of concepts, this paper is written to re-kindle the tradition of presenting the precise quantitative reasoning to the reader.

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2. GENERAL CELLULAR RAMIFICATIONS

2.1. The Resting Membrane and Action Potential

An action potential whose net change in voltage is 120 mV (1.2×10^{-1} V) imparts to a unit charge of 1.6×10^{-19} As (Coulombs, C) an energy of 2.0×10^{-20} J. This quantum of energy is mediated from the initial transduction of extraneuronal energy to action potentials and then through the release of contents from presynaptic vesicles which in turn initiates changes within dendrites and soma of the stimulated neuron. This energy is equivalent to the value required to stack one base on a RNA ribbon. According to Wei [4] the duration of this addition and of the action potential is about 1 msec.

This quantum of 10^{-20} J is also maintained between the ions within the narrow circumferential shell of about 0.6 nm [5] associated with cell's resting membrane potential. The width of the ion channel can be seen as a topologically punctate protrusion of this width through the cell membrane. Empirical measurements indicate that the capacitance of cell membranes for most neurons and glial cells are within 10% of 1 microF/cm^2. Assuming a resting membrane potential difference of 70 mV across the membrane, the numbers of ions within this thin band can be calculated.

The surface area of a 10 um (micrometer) cell is ($4\pi r^2$) or $12.56 \times .25 \times 10^{-8}$ cm^2. With q (charge)=voltage times capacitance, then 70×10^{-3} V x 1×10^{-6} F/cm^2 is 7×10^{-8} C/cm^2. Hence a cell with a diameter of 10 um would display a charge of 3.14×10^{-6} cm^2 times 7×10^{-8} C/cm^2 or 2.20×10^{-13} C. Because each unit charge is 1.61×10^{-19} C, a total of 2×10^6 molecules and their charges contribute to the resting membrane potential.

The area occupied by each charge on the cell surface, assuming a thickness of only 1 charge within the approximately 1 nm shell, would be (3.14×10^{-6} cm^2) divided by 2×10^6 particles or 1.57×10^{-12} cm^2/charge. The square root of that value is the average distance between charges which is about 1.2×10^{-6} cm or 1.2×10^{-8} m or 12 nm. Consequently, the distance between each charge within the single layer of

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charges on the cell surface is within the same order of magnitude and coefficient as the thickness of the cell membrane (about 10 nm).

This similarity is not spurious. The classical electric force between the charges is $F=(q_a q_b)/(r^2\ 4pi\ e))$, where q_a and q_b are the two unit charges, r is the distance and e is permittivity constant. The force at the 12 nm distance between charges is $(1.61 \times 10^{-19}\ As)^2$ /$[(1.1 \times 10^{-8}\ m)^2 \times 12.56 \times 8.85 \times 10^{-12}\ C^2/Nm^2]$ or 1.8×10^{-12} N. This pN (picoNewton) value is within the range observed for intermolecular forces [6]. However energy is force over distance. The application of this force of 1.8×10^{-12} N over a distance of 1.2×10^{-8} m is 2.2×10^{-20} J. From this perspective the kinetic energy associated with each action potential on charges is simply the conservation of the potential energy between the charges.

The energy can be derived by the product of the voltage and current dipole divided by velocity of the electrons. Assuming a current dipole of 20 fA m or 2×10^{-14} A m [7] the velocity of a unit charge of 1.6×10^{-19} A s would be about 1×10^5 m/s. This value is similar to the estimated velocity reported by Cosic [8] for free electrons to move along the DNA backbone. Consequently the product of the voltage of 10^{-1} V and the equivalent dipole moment of 2×10^{-14} A m divided by 1×10^5 m/s would about 2×10^{-20} J, the critical quantal unit.

This solution is complimented by the relationship to capacitance. Energy (J) is equal to the square of the dipole moment divided by the capacitance $[(A\ m)^2]/[(A^2s^4)/kg\ m^2)]$ and then multiplied by the square of the duration (s^2). The solution of $10^{-28}\ A^2m^2/10^{-14}$ F/um^2 is 10^{-14} J multiplied by s^2. To obtain 10^{-20} J the value for s must be 10^{-3} sec (1 msec), the typical range of the duration of the action potential. Consequently the temporal duration of the process involved with the basic mediation of digital information through brain space is convergent with the quantum of 10^{-20} J.

The continuity of the 10^{-20} J is evident during the intersynaptic transformation of an action potential to the release of chemical species from vesicles. The current I_i associated with a single post-synaptic potential with a current dipole moment (Q) of 20×10^{-15} A m s and the length constant of a dendrite [7] of about 0.2 mm (2×10^{-4} m) would be the quotient of 1×10^{-10} A. With 1.6×10^{-19} A s per charge, this means there are 10^9 charges involved over 1 sec or 10^6 charges within 1 msec for 1 channel or the requirement of between 100 and 1,000 ion channels over periods of 1 to 10 msec. The product of voltage, current, and time is energy. Either the product of 10^{-6} V, 10^{-10} A and 10^{-4} s (the order of magnitude of intersynaptic diffusion time for classical neurotransmitters) or the product of 10^{-7} V, 10^{-10} A and 10^{-3} s results in a value of 10^{-20} J.

The hypothesis of serial quanta, whose temporal patterns define the information within the biosystem, would require equivalent values within the next step in the sequence: receptors. Ionotropic glutamate receptors, that mediate most of the fast excitatory neurotransmission of the brain, manifest as bilobular proteins with a cleft between the two lobes. Full agonists result in an interlobe hydrogen bond between Glu402 and Thr686 of the protein [9] whereas antagonists do not produce this conformation.

The hinge motion subsequent to the sequestering of the agonist (glutamate binding) is associated with an energy change estimated to be 8.8 kJ/mole [9]. This is equivalent to about 1.5×10^{-20} J per molecule. Glutamate neurons often display a resting membrane potential closer to threshold, a feature that encourages burst-firing. Consequently, the slight difference in coefficient would reflect the proportional reduction in absolute change in voltage associated with these action potentials.

2.2. Metabolic Conservation

If the source of the energy within the brain is primarily derived from glucose, then the 10^{-20} J unit should be reflected in this metabolism. With an average glucose oxidation of 35 microMoles/min/g of tissue [10] a brain of 1.35 kg would use $.35 \times 10^{-6}$ M/min/g x 1.66×10^{-2} min/s x 1.35×10^3 g or $.78 \times 10^{-5}$ M/s. If one mole of glucose produces 2.87×10^6 J, then this value multiplied by $.78 \times 10^{-5}$ M/s indicates the whole brain volume would employ on average about 22 J/s or generate 22 Watts. The efficiency ratio of glucose metabolism would only affect the coefficient.

The energy density per cc of tissue, assuming 1 gm=1 cc because the specific gravity of brain tissue approaches unity, would be 1.47×10^{-2} J/cc or J/g per sec. With the area of the cell membrane being 3.14×10^{-6} cm^2 for a cell with a width of 10 um and a thickness of 1×10^{-6} cm (10 nm) the volume is 3.14×10^{-12} cc. The potential distribution of energy from glucose metabolism within this shell would be 3.14×10^{-12} cc times 1.47 J/cc or 4.61×10^{-14} J.

Because the energy involved with the distances between charges that contribute to a membrane potential of 70 mV is 1.12×10^{-20} J, this means that the membrane could "store" or dynamically transport approximately 4.61×10^{-14} J/1.12×10^{-20} J or 4×10^6 charged units. This is the order of magnitude of the numbers of ions required to maintain the resting membrane potential. The congruence of values suggests that the energy is conserved even within metabolic domains and that the "charge separation" energy may not be simply "electrostatic" but instead based on glucose derived thermal energy or some shared source of variance creating both.

The validity of these calculations and concept is suggested by the relationship between energy density within the cell and the numbers of functional molecules that it contains. With a cell volume of 5.23×10^{-10} cc (10 um diameter) and 20 J/1300 cc of brain volume, the average energy per cell volume would be about 10^{-11} J. If each molecule is carrying successive quanta of 10^{-20} J then about 10^9 molecules could be maintained. This is equivalent to the numbers of supraBoltzman-energy requiring enzymes and nucleotides within cells, including the neuron [11]. This number of molecules within the aqueous environment per cell volume would be equivalent to an average concentration of between 10 to 100 mM.

2.3. Cell-Cell Adhesion Forces

Cells are constantly exposed to minute time-varying mechanical forces evoked by intrinsic contractions or by a variety of environmental stimuli. The conversion of physical signals, such as contractile forces or mechanical perturba-

tions, into events mediated by chemical signalling is a fundamental cellular process. The interfaces, focal adhesions, occur within the cell-extracelluar matrix.

According to Bershadsky [12], the stress forces exerted by cells at focal adhesions, as obtained by several methods, average about 5 x 10^{-9} N/microm^2. The multiplication of the volume (um^3) in which this pressure occurs results in energy. If the quantum of 10^{-20} J is assumed, then the volume required for this force would be .42 x 10^{-11} microm^3, the cube-root of which is .16 x 10^{-3} microm or .16 nm. This width is within the range of the distance of atomic bonds, particularly covalent bonds (0.15 nm) rather than ionic (.25 nm), hydrogen (.30 nm) or van der Waal (.35 nm) forms. This solution suggests the importance of the 10^{-20} J quantum as a fundamental unit of interaction not only within cells but between cells.

3. EXPERIMENTAL EXAMPLES OF 10^{-20} J TRANSFORMATIONS

If there are essential quanta of transfer of information in biochemical reactions, the solutions should be evident in any process for which sufficient details are available. An example from three classes of processes demonstrates the validity of the concept. The first involves the authors research with measurement of quantum emission from cells in culture. The second involves the transfer of quanta, as chemical reactions, in serial steps of phosphorylation within general molecular signalling pathways. The third involves the transfer of a quantum, as light, in chromophores.

3.1. Direct Measurements of Photon Emissions From Cell Cultures

For the last two years we [13] have been obtaining measurements from photomultiplier tubes (PMT) to discern the intrinsic activity of cells in culture. Cell types have included BCL-16 (mouse melanoma), HEK (Human Embyronic Kidney), HSG (Human Salivary Gland), SK-Mel (Human Melanoma), THP and U937 (monocytic-like leukaemia) and HELA. In more than 100 trials, cells were removed from standardized incubation (37 deg C) and maintained for 12 hrs in a darkened room at room temperature (20 deg C). The changes in energy emission are conspicuous with peaks over several hours corresponding to alterations in membrane potentials. PMT measurements from media only displayed no fluctuations.

The plastic dishes containing the cells were placed over the aperture of the photomultiplier tube and the quantified emissions were recorded as changes in mV three times per sec by laptap computers. The specific values were extrapolations from calibration by LEDs at fixed distances and verified with sensitive luxmeters. Staining with acridine orange and ethidium bromide after removal from the experimental setting demonstrated the cell membranes had remained functional for eight hours after removal from incubation. After 24-hr diminished selective permeability of the membrane was clearly evident by the density of ethidium bromide. Trypan blue showed a small proportion of dead cells.

The most consistent and conspicuous observation has been the occurrence of about a 2 x 10^{-20} J functional unit from each cell. Within our experimental paradigm 1 unit fluctuation of the PMT metric was equivalent to 5.4 x 10^{-11} W/m^2. With a PMT aperture radius of 1 cm, the total energy is about 17 x 10^{-15} J/s per dish of cells and with 5 x 10^5 cells/dish this is equivalent to between 3 and 4 x 10^{-20} J/cell/s. Fourier and spectral analyses of either 2-hr or 12-hr trains of data (3 samples/s) revealed the strongest peak to be around 1 Hz. Even with an excessive estimate of 100% (factor of 2) opacity and loss the energy fluctuations per cell would be in the order of 2 x 10^{-20} J. The coefficient either doubled or was reduced by half when the numbers of cells were changed by that factor.

3.2. Phosphorylation and Specific Reaction Steps

Posttranslational modification of proteins by phosphorylation is a ubiquitous mechanism by which many cellular functions are controlled. Miranda *et al.* [14] reported that the energy difference between the phosphorylated and unphosphorylated subunits of phenylalanine hydroxylase was 11 kJ/mole or 1.8 x 10^{-20} J per site. They also showed discrete quanta in the change in energies for charge-charge interactions between the unphosphorylated and phosphorylated sites along the residual numbers (amino acid sequence). It is relevant that breaking of second shell hydrogen bonds, an essential step in the structural diffusion of protons (proton conduction) in water, is 1.8 x 10^{-20} J or 10.9 kJ/mol [15].

As predicted, thermodynamic parameters for the binding of peptides to the Grb (growth receptor bound) 7-SH2 domain was also equivalent to 2 x 10^{-20} J per site according to Spuches *et al.* [16]. The Grb7 family has been argued to facilitate more specialized signalling pathways. It is expressed particularly in the liver, kidney, and gonads [17] and is co-overexpressed with erbB2 in about 25% of all breast cancers [18]. The enhanced metabolism through electron chains converges with the 1.8 x 10^{-20} J "quantum" obtained from 1/2 the product of the mass of an electron (9.1 x 10^{-31} kg) and the square of average of the Cosic [8] velocity of 2 x 10^5 m/s for electrons moving along proteins.

3.3. Green Fluorescent Protein

Bioluminescence is light produced by a chemical reaction that occurs in an organism. Dinoflagellates are unicellar protists, primarily plankton. Zooxanthallae, the most common symbiotic dinoflagellates, are found in sponges, flatworms and jellyfish. Upon binding with calcium the green fluorescent protein (GFP) responsible for this phenomenon releases a quantum of energy perceived as blue light. The blue light is absorbed by a green fluorescent protein that in turn emits a green light. A classic example is the absorption of 395 nm and the release of 508 nm.

The energy difference, or quantal display, for these two wavelengths if one assumed 3 x 10^8 m/s for the velocity of light would be in the order of 10^{-18} J. However the velocity of light in water varies as a function of wavelength [19], with values of 2.147 x 10^8 m/s for 370 nm to 2.206 x 10^8 m/s at 520 nm. The difference in energy (J=Planck's constant multiplied by frequency) would require accommodating the different velocities in water when obtaining the specific frequencies. For 395 nm the value is 3.6212 x 10^{-19} J and for

508 nm the value is 2.8720 x 10^{-19} J. The net energy release per reaction would be 7.4 x 10^{-20} J. This would be sufficient for about 2 to 3 action potential equivalents. According to Meech [20] this is the number of low-threshold calcium spikes per sec displayed by the prototypical jellyfish Alganthа digitale.

4. BIOLOGICAL SIGNIFICANCE OF A QUANTAL MEDIATOR

4.1. The Potential Evolutionary Source

The source of the approximately 2 x 10^{-20} J quantum may emerge from the narrow range of temperature within which life exists. According to Wien's law, the wavelength ((0.29 cm-deg)/ T) at 310 deg K (37 deg C) would be 9.35 x 10^{-6} m (9.35 micrometers) which is conspicuously similar to the width of the average cell. This wavelength is 3.2 x 10^{13} Hz. When this frequency (1/s) is multiplied by Planck's constant, h (6.63 x 10^{-34} J), to obtain a classical energy value, the quantum of energy is 2.2 x 10^{-20} J.

4.2. Implications for Storage of Energy and Numbers of Action Potentials

The energy stored within a volume from a magnetic field is (B^2/u) multiplied by the volume where B is the strength of the field in Tesla, and u (mu) is the magnetic permeability=4pi x 10^{-7} N/A^2. For the volume (4/3 pi r^3) of soma with a diameter of 10 micrometers, the volume is 5.24 x 10^{-16} m^3. Consequently within the earth's static magnetic field of 50,000 nT or 50 microT (0.5 gauss), the energy stored within the magnetic field volume is (25 x 10^{-10} T^2)/(25 x 10^{-7} N/A^2) multiplied by 5.23 x 10^{-16} m^3 which equals 5.2 x 10^{-19} J.

With 2.0 x 10^{-20} J per action potential this allows for 32 action potentials per sec which is within the average range of pulses over protracted time. The increase in magnetic potential energy in the cell volume increases non-linearly such that a small neuron (5 microm wide) would average around 4 spikes/s while a larger neuron (50 microm) could exceed 1000. Consequently the volume of the soma could reflect the magnetic energy that is sufficient to set limits on the number of action potentials per second.

5. SUMMARY AND IMPLICATIONS

That information could be carried by quantized amounts of energy within a narrow range of energy suggests the existence of an intrinsic organization whose identification and isolation would allow a parsimonious understanding of what is now approaching an overwhelming complexity of molecular pathways. The existence of a very narrow energy range within which information is distributed is not unique. Many computer systems operate within the -5 to +5 V range. Values above or below this critical window are either destructive, interfering, or not effective.

If the critical component is the serial quanta of information within the space-time constraints of the cell, then the emphasis upon identifying "the" molecular pathways for normal conditions and for the treatment of disease may be less productive than anticipated. The many, apparent "parallel" systems and the extremely intricate pathways with multiple feedbacks, feed-forwards, and lateral effects, would be epiphenomenal. The emergence and maintenance of these myriad pathways would emphasize the biological and functional importance of having a reservoir "vehicles" available to insure the transport of biological quanta. It would be equivalent to transporting a person across a country. No matter which vehicle is employed, the individual being carried is the same person at the destination.

Secondly, every particle (mass) within the brain and other organs is also associated with a wave propagating through space. In other words for ever chemical sequence there should be an equivalent wave-sequence. As emphasized by de Broglie [21], matter waves are phase waves of the matter field associated with motions of quanta as they spread over the whole of space. An aggregate of particles that compose each organ should exhibit a macroscopic wave function operating within a collective mode similar to the propagation of wave of the matter field.

This assumption indicates that the information involved with the maintenance of cell function, particularly within the brain, can be strategically affected or "treated" through either particulate matter (chemical sequences) or the equivalent wave functions (electromagnetic patterns) that reflect the organization of this information in space and time, respectively. New and yet to be developed technologies that focus upon directly influencing the temporal pattern of biological quantum within the range of 10^{-20} J could be a more direct and efficient means of changing cell function and hence treating the physicochemical bases of diseases rather than attempting to isolate and to map the innumerable and different molecular signalling pathways that differ not only between cell lines but between types of the approximately 10 trillion cells within the body.

The approach of modern neural science [22] has implicitly assumed that neuronal resting potentials can be explained without the requirement for quantum mechanics. From this perspective the resting potential and the phenomena dependent upon it can be accommodated by the concrete application of the Nernst equation and Ohm’s law in the form of the Goldman-Hodgkin-Katz equation. When the membrane potential changes the energy associated with each ion changes accordingly.

However the third consideration derived from the concepts presented in this paper is that the intrinsic functions of all biosystems can be related to fundamental quantum properties, as originally postulated by Schrodinger [2] and Bohr [3]. If the energetic units by which information is generated and maintained within living systems are reflections or even identities with the essence that defines all of space and the forces within it, then the paradigms by which we view and understand "life" and its medicinal chemical treatment may require some modification.

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